Fothergill, R. T., Emmerson, A. C., Iyer, R., Lazarus, J., Whitbread, M., Nolan, J. P., Deakin, C. D., & Perkins, G. D. (2019). Repeated adrenaline doses and survival from an out-of-hospital cardiac arrest. *Resuscitation*, *138*, 316-321. https://doi.org/10.1016/j.resuscitation.2019.01.022

Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Repeated adrenaline doses and survival from an out-of-hospital cardiac arrest

Rachael T. Fothergill[a,g,*], *Amber C. Emmerson*[a], *Rajeshwari Iyer*[a], *Johanna Lazarus*[a], *Mark Whitbread*[b], *Jerry P. Nolan*[c,d,g], *Charles D. Deakin*[e,f], *Gavin D. Perkins*[g,h]

[a] *Clinical Audit and Research Unit, London Ambulance Service NHS Trust, London, United Kingdom*
[b] *Medical Directorate, London Ambulance Service NHS Trust, London, United Kingdom*
[c] *Bristol Medical School, University of Bristol, Bristol, BS8 1TH, United Kingdom*
[d] *Royal United Hospital, Bath, BA3 1NG, United Kingdom*
[e] *Respiratory BRU, University Hospital Southampton, SO16 6YD, United Kingdom*
[f] *South Central Ambulance Service NHS Foundation Trust, Otterbourne, United Kingdom*
[g] *Warwick Clinical Trials Unit, University of Warwick, Coventry, CV4 7AL, United Kingdom*
[h] *University Hospitals Birmingham NHS Foundation Trust, Heartlands Hospital, Bordesley Green East, Birmingham, B9 5SS, United Kingdom*

Abstract

Background: Adrenaline is the primary drug of choice for resuscitation from out-of-hospital cardiac arrest (OHCA). Although adrenaline may increase the chance of achieving return of spontaneous circulation (ROSC), there is limited evidence that repeated doses of adrenaline improves overall survival, and increasing evidence of a detrimental effect on neurological function in survivors. This paper reports the relationship between repeated doses of adrenaline and survival in a cohort of patients attended by the London Ambulance Service in the United Kingdom.

Methods: A retrospective review of OHCA treated by the London Ambulance Service over a one year period. Patients aged ≥18 years who received one or more doses of adrenaline (1 mg bolus) during resuscitation were included in the analyses. Outcomes described are survival to hospital discharge and survival to one year post-arrest.

Results: Over the one year study period, 3151 patients received adrenaline during OHCA. A significant inverse relationship was found between increasing cumulative doses of adrenaline and survival both to hospital discharge and one year post-arrest. No patients survived after receiving more than ten adrenaline doses.

Conclusion: Our study indicates that repeated doses of adrenaline are associated with decreasing odds of survival. There were no survivors amongst patients requiring more than 10 doses of adrenaline.

Keywords: Out-of-hospital cardiac arrest, Adrenaline, Epinephrine, Prehospital, Resuscitation, Repeated adrenaline doses

Introduction

The administration of adrenaline has been the cornerstone of treatment for out-of-hospital cardiac arrest (OHCA) for decades.[1] Resuscitation guidelines worldwide recommend the use of adrenaline, administered every 3–5 min, as part of advanced life support for cardiac arrest from all causes and all rhythms.[2–5]

Evidence for a short-term beneficial effect of adrenaline in achieving return of spontaneous circulation (ROSC) after an OHCA

* Corresponding author at: Clinical Audit and Research Unit, London Ambulance Service NHS Trust, 8-20 Pocock Street, London, SE1 0BW, United Kingdom.
E-mail address: rachael.fothergill@lond-amb.nhs.uk (R.T. Fothergill).
https://doi.org/10.1016/j.resuscitation.2019.01.022

has been reported in several observational studies and meta-analyses.[6–11] Notably, the recent randomised, double-blind PARAMEDIC2 trial, conducted within ambulance services in the United Kingdom (UK), found a higher rate of ROSC, with a small increase in survival to hospital discharge (<1%),[12] something supported by two previous randomised studies.[13,14]

Irrespective of any effect on survival, concern about the use of adrenaline in OHCA has been growing, with accumulating evidence indicating that its use may be harmful, particularly in terms of poorer neurological functioning.[7,9,15–17]

There are also questions around the quantities and numbers of doses of adrenaline given. One French study reported no difference in survival between repeated administrations of high-dose (5 mg) adrenaline and standard-dose (1 mg) adrenaline,[18] while reporting a slight increase in ROSC in the high-dose group. Another study from America reported higher rates of survival with less frequent administration of adrenaline than the recommended 3–5 min frequency of administration, indirectly suggesting that larger amounts of adrenaline may have poorer outcome.

Our study sought to examine the relationship between repeated (1 mg) doses of adrenaline and survival, and explore whether there is a point during OHCA after which the administration of further doses, as currently recommended, becomes futile.

Methods

Study design

A retrospective, observational analysis using anonymised data from the London Ambulance Service (LAS) cardiac arrest registry over a one-year period (1st April 2012 to 31st March 2013). Ethical approval was not required as this study used data routinely collected for clinical audit purposes.

Patient population

All adult patients (≥18 years of age) who experienced an OHCA of presumed cardiac aetiology, and received one or more doses of adrenaline (1 mg bolus) during resuscitation, were eligible for inclusion in this study.

Study setting

The LAS covers the geographical area of Greater London, UK, which spans approximately 620 square miles and serves a population of 8.4 million people.[19] During the study period, more than 1 million incidents were attended by the LAS,[20] with over 10,000 of these being OHCA.[21]

Calls identified as 'cardiac arrest' (using the advanced Medical Priority Dispatch System) receive the highest level response, with a minimum of two emergency vehicles, staffed by at least one paramedic (trained in advanced life support), being dispatched to the incident.

All LAS clinicians operate to the Resuscitation Council (UK) guidelines,[2] which advise the administration of adrenaline (intravenous or intraosseous) for all initial rhythms during an OHCA. If the patient presents in ventricular fibrillation or pulseless ventricular tachycardia (VF/pVT), a 1 mg bolus of adrenaline is administered after 3 unsuccessful defibrillation attempts, whereas for non-shockable rhythms (pulseless electrical activity (PEA) or asystole) a 1 mg bolus of adrenaline is administered as soon as possible. If the cardiac arrest persists, a further dose of adrenaline is advised every 3–5 min with no upper dose limit until either ROSC is achieved and the patient is handed over to hospital, or the resuscitation attempt is terminated. If ROSC is achieved, local LAS protocol allows a lower dose of adrenaline (0.1 mg bolus) to be administered to maintain the patient's blood pressure and prevent re-arrest.

Data collection

Data were obtained from the LAS Out-of-Hospital Cardiac Arrest Registry that collates patient, process, treatment and outcome information from multiple sources (including emergency dispatch call logs, and ambulance service and hospital clinical patient records) to provide a comprehensive clinical record for each OHCA. Characteristics and outcomes recorded include: patient demographics, location of arrest, presenting cardiac rhythm, bystander intervention, pre-hospital resuscitation methods, ROSC and survival to hospital discharge. Long-term outcome, with survival up to 1 year post-arrest, was obtained from NHS Digital Summary Care Records.

Data analysis

Data analysis and statistics were performed using Excel (Microsoft, Redmond, WA), SPSS v23 (IBM, Armonk, NY) and R 3.5.1 (A Language and Environment for Statistical Computing). Statistical significance was accepted when $p < 0.05$.

The association between percentage survival (to hospital discharge and to one year post-arrest) and independent explanatory variables was assessed using a step-wise multivariate logistic regression model. We first undertook univariate logistic regressions on all known predictors of survival (age, sex, adrenaline dose group, initial shockable rhythm, time from EMS call to first adrenaline dose, ROSC, bystander CPR, and witness status). We then built a step-wise multivariate regression model starting with the predictor that had the strongest association with the outcome based on the partial F-tests obtained from the regression. At each step we added the predictor that had the next strongest association or excluded the predictor that no longer explained the outcome. We stopped this procedure when no more predictors could be added or removed, and this is the final model upon which the results are based. Collinearity between the predictors was assessed by calculating the variance inflation factor (VIF) for each predictor and excluding those variables that had a VIF greater than 5. No predictor met this criterion and therefore none were removed from analysis based on collinearity. The number of doses of adrenaline were categorised into three categories, 1 dose, 2 doses, and >3 doses in the multivariate analysis.

When presenting results, continuous variables are presented as means ± standard deviation (SD) and categorical variables are reported as counts with relative frequencies. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) obtained from the multi-variable binomial logistic regression after controlling for potential confounders were used to interpret associations between variables and outcomes.

Results

Resuscitation was attempted for 4466 OHCA patients; with 3151 (71%) meeting the criteria for inclusion in the study (see Fig. 1). In total, 137

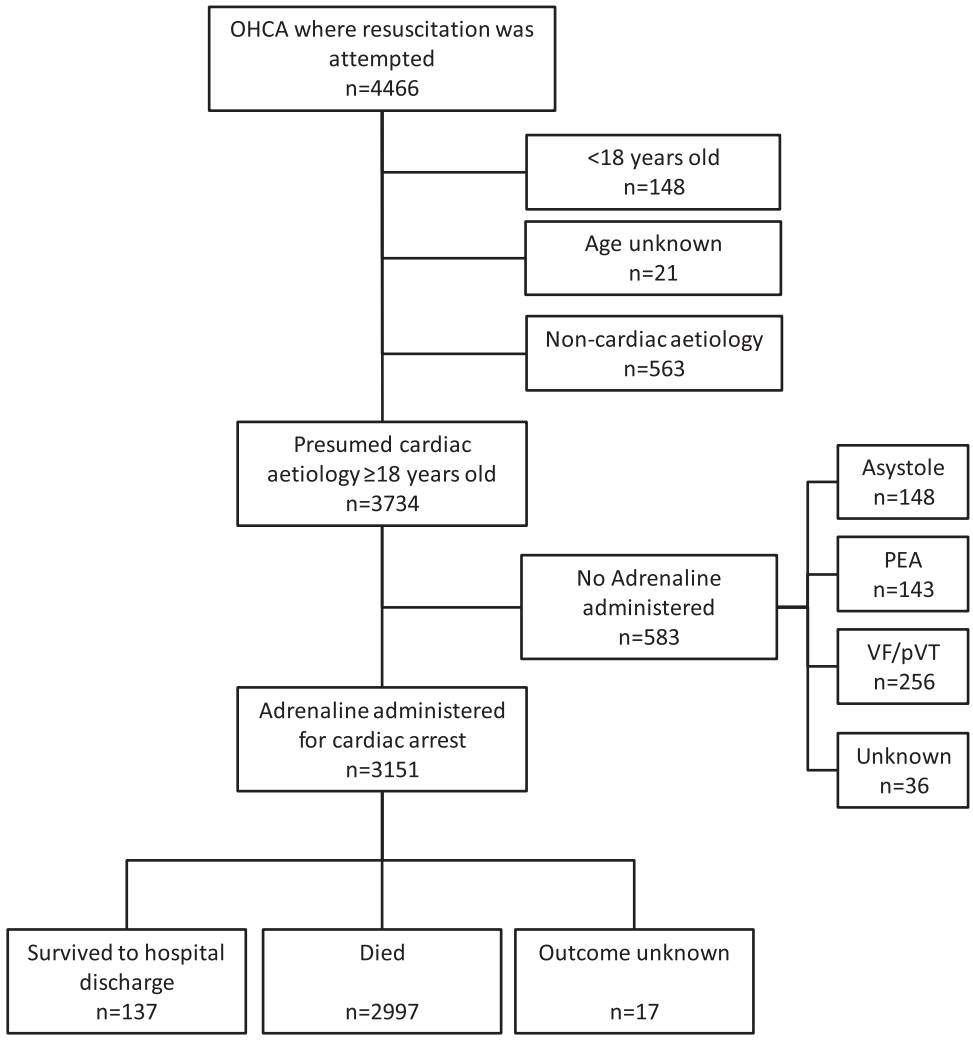

Fig. 1 – Overview of cases meeting our inclusion criteria and outcomes.

(4.3%) patients survived to be discharged from hospital, with 108 of 122 patients (88.5%; with 15 lost to follow up) still alive at one year (representing 3.4% overall). Patient demographics and key event characteristics based on patient outcome are summarised in Table 1. Compared to non-survivors, those who survived to one year had almost four fewer doses of adrenaline on average ($p < 0.001$), presented with an initial shockable rhythm (VF/VT) ($p < 0.0001$), were more likely to have had a witnessed arrest ($p < 0.001$), received a higher number of shocks ($p < 0.001$) and had an 'EMS call' to 'administration of first adrenaline dose' interval that averaged 5 min faster ($p < 0.001$).

Each 1 min of delay from 'EMS' call to 'administration of first adrenaline dose' was associated with a 7% reduction in survival (OR = 0.93; CI = 0.91, 0.96; $p < 0.0001$) to both hospital discharge and one year post arrest. However, this association was no longer significant after adjusting for other covariates in the multivariate regression model (AOR = 0.98; CI = 0.95, 1.00; $p = 0.09$).

Association of repeated doses of adrenaline and survival

The relationship between repeated adrenaline doses and survival both to hospital discharge and to one year post-arrest is presented in Fig. 2 and Supplementary Table 1. The number of adrenaline doses administered had a negative association with both measures of survival. Survival to hospital discharge was approximately 20% with one dose of adrenaline, rapidly declining to less than 2% at five or more doses. Survival to one year followed a similar pattern. There were no survivors amongst patients who received more than 10 doses of adrenaline.

While there were variables listed in Table 1 that were significantly associated with survival at the univariate level, only adrenaline dose group, presence of an initial shockable rhythm, age and sex could significantly predict survival in the step-wise regression model. Therefore we present association of adrenaline dose group with survival after adjusting for the significant confounders, initial shockable rhythm, age and sex.

Multivariate analysis revealed that when adjusted for the effects of age, sex, and an initial shockable rhythm, three or more doses of adrenaline were associated with an 85% decrease in the likelihood of surviving to hospital discharge (AOR = 0.15; CI = 0.09, 0.26; $p < 0.0001$) and an 82% decrease in surviving to one year (AOR = 0.18; CI = 0.1, 0.11; $p < 0.0001$). Full analysis results are detailed in Table 2.

Two patients (out of 190; 1.1%) who received 9 doses of adrenaline, and a further 2 patients (out of 224; 0.9%) who received

Table 1 – Patient demographics and key event characteristics for out-of-hospital cardiac arrests (OHCA) where one or more dose of adrenaline (1 mg) was administered during resuscitation. Univariate analysis was used to compare patients who survived to 1 year and those who died. 33 cases were excluded from analysis due to unknown outcomes. SD, standard deviation; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia; PEA, pulseless electrical activity.

Characteristics	Outcome at hospital discharge			Outcome at one-year		
	Survived n = 137	Died n = 2997	p-value	Survived n = 108	Died n = 3011	p-value
Age (years), mean ± SD	57.7 ± 15.4	70.4 ± 16.8	<0.001	57.1 ± 15.3	70.4 ± 16.8	<0.001
Sex (male), n (%)	118 (86.1)	1821 (60.8)	<0.001	92 (85.2)	1834 (60.9)	<0.001
Witnessed arrest, n (%)	112 (81.8)	1879 (62.7)	<0.001	87 (80.6)	1891 (62.8)	<0.001
Bystander	89 (65.0)	1445 (48.2)		68 (63.0)	1455 (48.3)	
EMS clinician	23 (16.8)	434 (14.5)		19 (17.6)	436 (14.5)	
Not witnessed	25 (18.2)	1116 (37.2)		21 (19.4)	1118 (37.1)	
Bystander CPR, n (%)	65 (47.4)	1277 (42.6)	0.263	51 (47.2)	1282 (42.6)	0.338
Defibrillation performed, n (%)						
Pre-EMS defibrillation	3 (2.2)	25 (0.8)	0.099	1 (0.9)	26 (0.9)	0.945
EMS defibrillation	108 (78.8)	991 (33.1)	<0.001	94 (87.0)	996 (33.1)	<0.001
Number of shocks, mean ± SD	3.5 ± 3.1	1.7 ± 3.7	<0.001	3.9 ± 3.1	1.7 ± 3.4	<0.001
Initial arrest rhythm, n (%)						
Asystole	18 (13.1)	1671 (55.8)	<0.001	9 (8.3)	1678 (55.7)	<0.001
VF/pVT	101 (73.7)	520 (17.4)		88 (81.5)	524 (17.4)	
PEA	17 (12.4)	802 (26.8)		10 (9.3)	805 (26.7)	
Unknown	1 (0.7)	4 (0.1)		1 (0.9)	4 (0.1)	
Successful intubation, n (%)	49 (35.8)	1241 (41.4)	0.108	34 (31.5)	1251 (41.5)	0.036
Dose of adrenaline, Mean ± SD	2.6 ± 1.9	6.2 ± 3.4	<0.001	2.6 ± 1.9	6.2 ± 3.4	<0.001
Time from EMS call to first Adrenaline dose (MM:SS), Mean ± SD	21:39 ± 11:0	26:51 ± 13:3	<0.001	21:08 ± 10:4	26:39 ± 13:3	<0.001

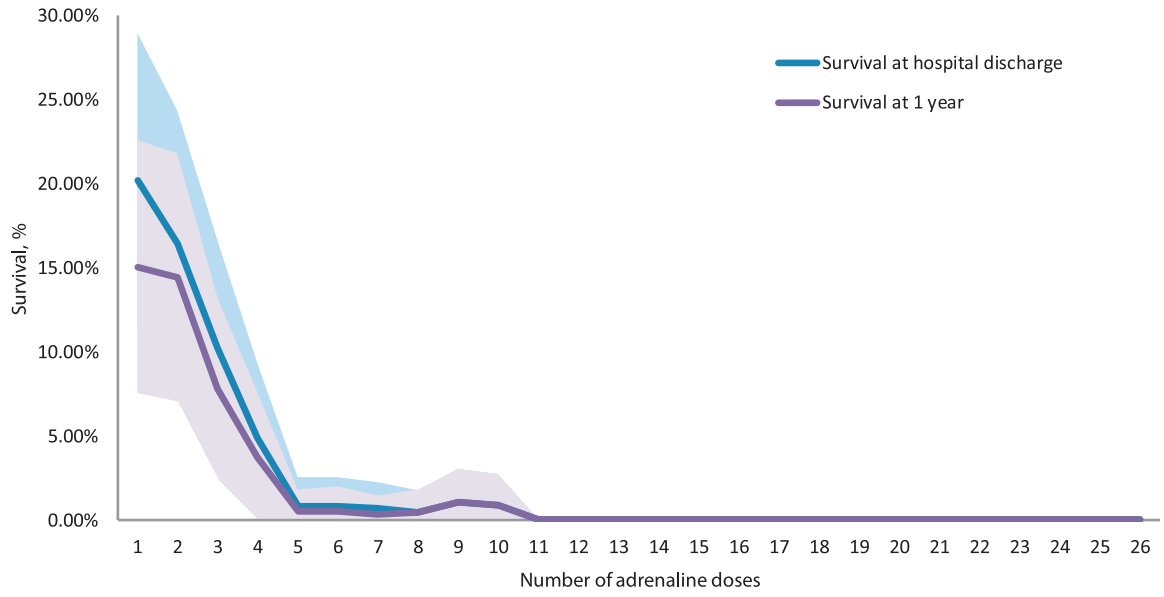

Fig. 2 – Relationship between the number of adrenaline doses and percentage survival to hospital discharge and survival to 1-year post-arrest. Shaded regions represent 95% confidence interval. 33 unknown outcomes were excluded from analysis.

exactly 10 doses of adrenaline, survived to hospital discharge and were still alive at one year (see Supplementary Table 2 for details of these patients). The first dose of adrenaline was administered to all four patients in less than 13 min from initiation of CPR, well within the overall average (15 min). All cases had an end-tidal carbon dioxide ($ETCO_2$) value over 20 mmHg with Cases 1 and 3 exceeding 30 mmHg. Case 2, 3 and 4 had intermittent ROSC during resuscitation, with Cases 1, 2 and 3 achieving a stable ROSC which was sustained from the arrest location to hospital handover. In addition, the three patients who suffered a myocardial infarction (Cases 1, 2 and 4) were conveyed by ambulance directly to a specialist heart attack centre for coronary intervention.

Table 2 – Adjusted odds ratios (AOR) for survival to hospital discharge and 1 year post-arrest. Multivariate analysis was used to control for potential confounders listed on Table 1.

	AOR (95% CI)[a]	*p*-value
Outcome at hospital discharge		
1 dose of adrenaline	Reference	(-)
2 doses of adrenaline	0.7 (0.39, 1.28)	0.67
≥3 doses of adrenaline	0.15 (0.09, 0.26)	<0.0001
Initial shockable rhythm (not present)	Reference	(-)
Initial shockable rhythm (present)	9.83 (6.1, 15.86)	<0.0001
Age	0.96 (0.95, 0.97)	<0.0001
Sex (Male)	Reference	(-)
Sex (Female)	2.98 (1.66, 5.33)	0.0002
Outcome at 1 year		
1 dose of adrenaline	Reference	(-)
2 doses of adrenaline	0.85 (0.46, 1.62)	0.62
≥3 doses of adrenaline	0.18 (0.1, 0.33)	<0.0001
Initial shockable rhythm (not present)	Reference	(-)
Initial shockable rhythm (present)	14.27 (8.26, 24.6)	<0.0001
Age	0.96 (0.95, 0.98)	<0.0001
Sex (Male)	Reference	(-)
Sex (Female)	2.49 (1.36, 4.58)	0.003

SD, standard deviation; CI, confidence interval.
[a] An adjusted odds ratio above 1.0 favors survival.

A total of 267 patients received more than 10 doses of adrenaline, and none survived. Using the 'rule of three'[22] our study predicts that more than 10 doses of adrenaline will result in no more than 1.1% (95% CI 0–1.1) of patients surviving to hospital discharge and one year post arrest.

Discussion

This study sought to describe the association between repeated doses of adrenaline and survival. We found that three or more doses were associated with a significant reduction in the odds of surviving to both hospital discharge and to one year post-arrest. The decline in survival was evident up to five cumulative doses of adrenaline, at which point the relationship flattened due to very few survivors, with no survivors after ten doses. The significant inverse relationship between cumulative doses of adrenaline and survival persisted even after adjusting for potential confounders using multivariate analysis.

These results support the findings of Glover et al.[23] who described an independent negative association between the probability of survival to hospital discharge and adrenaline dose in the US and Canada. We found four patients who, despite a higher number of adrenaline doses (9 or 10 doses), were still alive one year post-arrest. However, it is likely that the favourable factors observed (which included a reversible cause of arrest, conveyance to a specialist centre, and a short time to first adrenaline dose) contributed to their survival.

While in our study, 'EMS call' to 'administration of first adrenaline dose' interval was not significantly associated with survival after adjusting for confounders, previous studies have identified a relationship between time to first dose of adrenaline and survival[24–28] in their multivariate models. Hubble et al observed a 4% reduction in the odds of obtaining ROSC for every one minute delay from emergency call to administration of a vasopressor.[24] Two other studies suggested that, when administered within 20 min of the emergency call, repeated doses of adrenaline were associated with improved neurological outcome for witnessed cardiogenic OHCA.[25,26] Hayashi et al further demonstrated that for patients in VF/VT,[27] administration of adrenaline within 10 min of the emergency call was associated with better one-month neurological outcome.[28] In our study, those who survived to one year had an 'EMS call' to 'first adrenaline dose' time interval that was, on average, five minutes faster compared to those who died. It is to be noted however, that variables used to build multivariate models differed in all these studies and perhaps could explain the difference in results.

Being an observational study, we were unable to separate the effect of the number of adrenaline doses, from the length of time a patient was in cardiac arrest and the severity of their condition, both of which are known to influence outcome.[29] As such, our findings must be interpreted with caution. It is likely that cumulative doses of adrenaline are a proxy for cardiac arrest duration, which is associated with increasingly poor outcome, a phenomenon that has been termed 'resuscitation time bias'.[29] However, given that adrenaline increases the likelihood of achieving ROSC, these two variables are heavily interdependent. The observed effects may also be attributed to other unknown confounders.

There are further limitations in the data available for our study. We were unable to obtain neurological outcomes from hospitals, and this would have provided a valuable insight into the neurological effects of cumulative adrenaline doses and the quality of life for OHCA survivors. Technological limitations within our EMS system prevented defibrillator downloads from being available for analysis; these data would have enabled us to assess the quality of CPR, something which may have impacted on drug delivery and subsequent efficacy.[30]

Despite the limitations, our findings support the need for further research into the efficacy, timing and dosage of adrenaline during resuscitation. Current guidelines recommend administration of adrenaline (1 mg) every 3–5 min[2]; however, in-hospital studies suggest that a less frequent dosing strategy may increase survival[31] and could reduce development of secondary VF/VT.[32] One study comparing high-dose adrenaline (15 mg) with the standard dose (1 mg), documented an increase in ROSC and survival to hospital admission with the higher dose.[33] In contrast, Frisk et al. investigated a lower adrenaline dose (0.5 mg), which did not affect survival to hospital discharge or favourable neurological outcome for OHCA patients.[34] It is clear that the optimum dose of adrenaline is a knowledge gap that needs further investigation.[35]

Conclusion

Our study indicates that repeated doses of adrenaline are associated with decreasing odds of survival. There were no survivors amongst patients requiring more than 10 doses of adrenaline.

Conflict of interest

None.

Acknowledgements

We would like to thank Matthew Dodd for providing statistical advice and Professor Simon Gates for providing comments on the draft manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.01.022.

REFERENCES

1. Callaway CW. Questioning the use of epinephrine to treat cardiac arrest. JAMA 2012;307:1198–200.
2. Resuscitation Council, UK; 2015. www.resus.org.uk/ [Accessed September 2017]. Available at: https://www.resus.org.uk/resuscitation-guidelines/adult-advanced-life-support/.
3. Soar J, Nolan JP, Bottiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: section 3. Adult advanced life support. Resuscitation 2015;95:100–47.
4. The Australian and New Zealand Committee on Resuscitation (ANZCOR). Guideline 11.5 - medications in adult cardiac arrest. 2016. . [Accessed November 2017] https://resus.org.au/guidelines/.
5. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S444–64.
6. Atiksawedparit P, Rattanasiri S, McEvoy M, Graham CA, Sittichanbuncha Y, Thakkinstian A. Effects of prehospital adrenaline administration on out-of-hospital cardiac arrest outcomes: a systematic review and meta-analysis. Crit Care 2014;18:463.
7. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. JAMA 2012;307:1161–8.
8. Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. Resuscitation 2014;85:732–40.
9. Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Increased return of spontaneous circulation at the expense of neurologic outcomes: is prehospital epinephrine for out-of-hospital cardiac arrest really worth it? J Crit Care 2015;30:1376–81.
10. Ono Y, Hayakawa M, Wada T, Sawamura A, Gando S. Effects of prehospital epinephrine administration on neurological outcomes in patients with out-of-hospital cardiac arrest. J Intensive Care 2015;3:29.
11. Reardon PM, Magee K. Epinephrine in out-of-hospital cardiac arrest: a critical review. World J Emerg Med 2013;4:85–91.
12. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med 2018;379:711–21.
13. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation 2011;82:1138–43.
14. Olasveengen TM, Wik L, Sunde K, Steen PA. Outcome when adrenaline (epinephrine) was actually given vs. not given - post hoc analysis of a randomized clinical trial. Resuscitation 2012;83:327–32.
15. Dumas F, Bougouin W, Geri G, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? J Am Coll Cardiol 2014;64:2360–7.
16. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA 2009;302:2222–9.
17. Patanwala AE, Slack MK, Martin JR, Basken RL, Nolan PE. Effect of epinephrine on survival after cardiac arrest: a systematic review and meta-analysis. Minerva Anestesiol 2014;80:831–43.
18. Gueugniaud PY, Mols P, Goldstein P, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. N Engl J Med 1998;339:1595–601.
19. Office for National Statistics. Annual mid year population estimates: 2013. 2014. . [Accessed September 2017] www.ons.gov.uk.
20. Andersen LW, Berg KM, Saindon BZ, et al. Time to epinephrine and survival after pediatric in-hospital cardiac arrest. JAMA 2015;314:802–10.
21. London Ambulance Service NHS Trust. Cardiac arrest annual report 2012-2013. 2013. . [Accessed November 2017] www.londonambulance.nhs.uk/about_us/publications.
22. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983;249:1743–5.
23. Glover BM, Brown SP, Morrison L, et al. Wide variability in drug use in out-of-hospital cardiac arrest: a report from the resuscitation outcomes consortium. Resuscitation 2012;83:1324–30.
24. Hubble MW, Johnson C, Blackwelder J, et al. Probability of return of spontaneous circulation as a function of timing of vasopressor administration in out-of-hospital cardiac arrest. Prehosp Emerg Care 2015;19:457–63.
25. Sagisaka R, Tanaka H, Takyu H, Ueta H, Tanaka S. Effects of repeated epinephrine administration and administer timing on witnessed out-of-hospital cardiac arrest patients. Am J Emerg Med 2017;35:1462–8.
26. Tanaka H, Takyu H, Sagisaka R, et al. Favorable neurological outcomes by early epinephrine administration within 19 minutes after EMS call for out-of-hospital cardiac arrest patients. Am J Emerg Med 2016;34:2284–90.
27. Hayashi Y, Iwami T, Kitamura T, et al. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. Circ J 2012;76:1639–45.
28. Nakahara S, Tomio J, Nishida M, Morimura N, Ichikawa M, Sakamoto T. Association between timing of epinephrine administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: a population-based prospective observational study. Acad Emerg Med 2012;19:782–92.
29. Andersen LW, Grossestreuer AV, Donnino MW. "Resuscitation time bias" - a unique challenge for observational cardiac arrest research. Resuscitation 2018;125:79–82.
30. Pytte M, Kramer-Johansen J, Eilevstjonn J, et al. Haemodynamic effects of adrenaline (epinephrine) depend on chest compression quality during cardiopulmonary resuscitation in pigs. Resuscitation 2006;71:369–78.
31. Warren SA, Huszti E, Bradley SM, et al. Adrenaline (epinephrine) dosing period and survival after in-hospital cardiac arrest: a retrospective review of prospectively collected data. Resuscitation 2014;85:350–8.
32. Straznitskas AD, Wong S, Kupchik N, Carlbom D. Secondary ventricular fibrillation or pulseless ventricular tachycardia during cardiac arrest and epinephrine dosing. Am J Crit Care 2015;24:e22–7.
33. Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. JAMA 1992;268:2667–72.
34. Fisk CA, Olsufka M, Yin L, et al. Lower-dose epinephrine administration and out-of-hospital cardiac arrest outcomes. Resuscitation 2018;124:43–8.
35. Kleinman ME, Perkins GD, Bhanji F, et al. ILCOR scientific knowledge gaps and clinical research priorities for cardiopulmonary resuscitation and emergency cardiovascular care: a consensus statement. Circulation 2018;137:e802–19.